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10/523,253	01/26/2005	Samual Weiss	16601-021US1	8661

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,253	WEISS, SAMUAL	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *19-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 15, 24 and 35 have been amended in the amendment filed 2/26/2007. Claims 19-40 have been withdrawn. Claims 1-18 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 10-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of producing oligodendrocytes from multipotent neural stem cells isolated from mouse embryos, does not reasonably provide enablement for a method of producing oligodendrocytes from all types of neural stem cells isolated from any mammal at any developmental stage while the cells are located in a mammal (i.e. *in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation *United States v. Telectronics*, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These

factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Scope of the claims. The claims are drawn to an *in vivo* method of differentiation of neural stem cells into oligodendrocytes using an oligodendrocyte promoting factor (OPF), which encompasses a very broad genus of any kind of mammal including humans with demyelinating disease. The claims encompass an embodiment in which the OPF would be administered to the mammal to differentiate the cells. The claims also encompass an embodiment comprising transplanting the stem cells into the mammal and administering an OPF in an effective amount.

2) State of the Art. Chandran and Compston (J. Neurol. Sci., 2005 Vol. 233, pages 179-181) review the potential for neural stem cell in treatment of demyelination repair. Chandran and Compston teach that such an approach requires a large and enriched numbers of human oligodendrocyte precursors to study their biology and remyelinating potential. Chandran and Compston teach that there is considerable need for improved understanding of the signaling requirements that underlie the generation of oligodendrocytes from neural stem cells (see page 179, right column, for example). Chandran and Compston also teach that there are interspecies differences in oligodendrocyte potential of neural precursors which cautions the extent to which data from rodents can reliably made to the human system (see page 180, right column, in particular).

Imitola et al (Physiol. Genomics, 2003, Vol. 14 pages 171-197) also review the potential for neural stem cell in treatment of demyelination repair. Imitola et al teach that

the subventricular zone of the brain is a source of neural stem cells (see page 172, right column). Imitola et al teach that new oligodendrocytes seem to originate from oligodendrocyte precursors by way of neural stem cells, since oligodendrocyte precursors can be identified by markers in the adult forebrain and spinal cord.

3) Unpredictability of the art. The unpredictability of a method to produce oligodendrocytes from neural stem cells in a mammal by administering an OPF is manifested in the ability of the OPF to specifically affect the neural stem cells. Imitola et al teach that in order to exploit the biological properties of precursors and to promote their differentiation in desired directions, a better understanding of the molecular pathways governing the neural stem and oligodendrocyte precursors during development and disease is required (see page 187, left column, 2nd paragraph). The claimed method encompasses an embodiment in which the OPF is administered systemically or locally to the mammal. Imitola et al teach that the continuous local infusion of exogenous cytokines may have positive effects on recruiting endogenous precursors but that it is not clear how long such manipulation is required in the clinical setting to induce an effect. Imitola et al also teach that a continuous infusion of factors may induce hyperplasia and raises questions about the tumorogenic potential of such manipulations. Imitola et al teach that some trophic factors have pleiotrophic effects on the brain, which may work at cross purposes with each other. In the case of a mammal with a disease such as a demyelinating disorder, implanting exogenous cell may be problematic unless the cells have been engineered to be resistant to the environment that is causing the injury (see page 187, right column, for example). The instant

specification contemplates practicing the claimed method in demyelinating disorders with areas of demyelination in plaque-like structures. However, Imitola et al teach that addressing multiple lesions that extend throughout the central nervous system is a daunting prospect even with extensively migratory stem cells. Further Imitola et al teach that the size of some lesions may overcome the capacity for endogenous precursor cells to repair damage. Imitola et al caution that careful strategic planning and extensive animal testing will be required before clinical studies can be entertained. Imitola et al teach that the development of methods for noninvasive monitoring of the neural stem cell transplant is required. Imitola et al summarize that more research is needed to understand the signaling pathways for obtaining highly specific molecular targets without inducing aberrant neurogenesis or tumorogenic proliferation. Imitola et al conclude that clearly further clinical application of transplantation of stem cells for producing cells for multiple sclerosis disorders (as contemplated by the specification) requires "a great deal of additional experimental research" (see page 189, left column, for example).

4) Amount of guidance provided. The specification discloses that the multipotent neural stem cell should be introduced into the mammal and an effective amount of at least one OPF would be administered to the mammal under conditions that resulting oligodendrocyte formation. The specification also discloses a method in which an effective amount of oligodendrocyte produced from neural stem cells using an OPF with a pharmaceutically acceptable carrier. The specification provides only general guidance that the cells can be administered systemically or *in situ* such as in a lateral

ventricle of the brain. The specification also discloses that the cells can be introduced into the brain or spinal cord and particularly at sites where axons have be demyelinated by disease. Applicants contemplate transplanting cells at the mirror image location of a target lesion in the opposite hemisphere, so that the cell would migrate to the corresponding location through the corpus callosum (see paragraph 0081). The specification provides only general guidance that the OPF can be administered via any suitable route, depending on the nature of the OPF. The specification does not provide specific guidance regarding dosages of any OPF to be administered to multipotent neural stem cells located in any mammal, including human mammals. The specification does not provide any guidance regarding how often the OPF would need to be administered to the neural stem cells in mammal in order to produce oligodendrocytes. The limitation of mammal encompasses mammals of any age and in any state of health. There is no guidance regarding whether there is any alteration in the method if the mammal is a neonate or is elderly. There is no guidance regarding whether there is any alteration in the method if the mammal is healthy, has been acutely injured or has had a demyelinating disease for many years. The specification does not provide sufficient guidance on how the skilled artisan would know if the oligodendrocytes had been produced. For example if an OPF was administered systemically to a human, the specification does not provide guidance to the skilled artisan to determine if the method was successful. The specification does not provide sufficient guidance so that the skilled artisan would know how to use the claimed method to produce oligodendrocytes

from multipotent neural stem cells without using excessive and undue trial and error experimentation.

5) Working examples. The specification provides examples of a method of producing oligodendrocytes *in vitro*. The specification does not provide any example of a method of producing oligodendrocytes in a mammal from multipotent neural stem cells by contacting them with an effective amount of an OPF when the stem cells are located in a mammal or specifically in the subventricular zone of a mammal.

6) Nature of the invention. The invention is drawn to a method to differentiate mammalian multipotent stem cells *in vitro* or *in vivo*, which encompasses stem cell therapy and is a complex and unpredictable aspect of science and medicine.

7) Level of skill in the art. The skill in the art is high, but given the state of the art, the unpredictability of the art, the lack of specific guidance and working examples, and scope and nature of the invention, the skilled artisan would have to practice excessive trial and error experimentation in order to be able to use the claimed method.

Given the above analysis of the factors which the Courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention to its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 6-9, 12, 14-15 and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Mehler et al (of record). Claims 7-8 are newly added to this rejection.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 12/28/2006 and for reasons outlined below.

Applicants submit that the cited passages of Mehler et al do not disclose or suggest providing G-CSF under conditions that result in production of oligodendrocytes from multipotent neural stem ceils. Mehler et al states on page 230, 4th, paragraph, that "[a]pplication of NT3, IGF1 and gp130-associated factors, either individually in combination, did not potentiate expression of any OL lineage species, However pretreatment, or simultaneous application of bFGF or PDGF-AA, alone or in combination, followed by tandem application of NT3, IGF1 and an individual gp130-related factor resulted in....maturation of OL [oligodendrocyte] species generated from the initial neural stem cell population." Therefore. it is impossible to determine whether G-CSF had any effect on neural stem cells based on the cited passages of Mehler. Applicants submit that assuming *arguendo* that when Mehler states "gp130-associated factors"' this includes G-CSF, then Mehler teaches away from the claims of the present

application by stating that G~CSF alone or in combination does not promote oligodendrocyte production from neural stem cells. Applicants submit that, in contrast, a colony-stimulating factor (GM-CSF) was provided to neural stem cells under conditions that promote production of oligodendrocytes (Figure 1 of the present application). Applicants submit that only the present application provides one of skill in the art with a method of producing oligodendrocytes from mammalian multipotent neural stem cells, comprising contacting the neural stem cells with at least one oligodendrocyte promoting factor under conditions that result in production of oligodendrocytes from multipotent neural stem cells.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive.

In their arguments, Applicants quote page 230, 4th paragraph of Mehler:

"[a]pplication of NT3, IGF1 and gp130-associated factors, either individually in combination, did not potentiate expression of any OL lineage species, However pretreatment, or simultaneous application of bFGF or PDGF-AA, alone or in combination, followed by tandem application of NT3, IGF1 and an individual gp130-related factor resulted in....maturation of OL [oligodendrocyte] species generated from the initial neural stem cell population."

It appears that this 4th paragraph of page 230 is describing several specific experimental conditions. There appear to be two trials in the lines quoted by the Applicants. One appears to be a trial in which only NT3, IGF1 and gp130-associated factors were added to the cells and subsequently did not produce any OL lineage species. A second trial appears to be one in which bFGF or PDGF-AA was applied to cells along with NT3, IGF1 and an individual gp130-related factor.

However, page 230, 4th paragraph also states:

"At the non-permissive temperature (39°C), application of a limited subset of growth factors from several cytokine subclasses (bFGF, PDGF-AA, IGF1, NT3; and gp130 receptor subunit-associated ligands; CNTF, LIF; OM; IL-6, IL-12, G-CSF) significantly increased survival and promoted cellular differentiation from neural stem cells of distinct OL progenitor populations".

This passage appears to describe a trial in which bFGF, PDGF-AA, IGF1, NT3; and CNTF, LIF; OM; IL-6, IL-12, G-CSF (gp130 receptor subunit-associated ligand) were all applied) and resulted in cellular differentiation from neural stem cells of distinct OL progenitor populations. This combination of factors includes G-SCF and therefore meets the limitation of the method of claim 1. The claimed method does not exclude the multipotent neural stem cells from contact with other oligodendrocyte promoting factors and the combination of bFGF, PDGF-AA, IGF1, NT3; and CNTF, LIF; OM; IL-6, IL-12, G-CSF produces differentiated cells. Although Mehler et al teach that other trials with a different combination of factors do not produce oligodendrocytes, it does not mean that all of Mehler et al teach away from the claimed method. Mehler et al teach that G-CSF was included as a gp130 receptor subunit associated ligands in subset of factors that produced differentiated cells, absent evidence to the contrary, it would have had an effect (i.e. an effective amount). Therefore the teaching of Mehler et al meets the limitations of the claimed method.

In the experiments taught, Mehler et al use an immortalized neural progenitor cell like from early postnatal mouse brain. In other experiments Mehler et al use brain tissue over a broad developmental time span including embryonic brain, postnatal brain and adult brain (see page 230, 3rd paragraph, page 220, 3rd and 4th paragraph, and page 221, 2nd paragraph, for example). Therefore, Mehler et al contemplate using mammalian

brain tissue from a non-embryonic mammal and an adult mammal and meet the limitation of claims 7-8.

Claims 1-2, 5, 12-15 and 17-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Tennekoon et al (U.S. Patent No. 6,673,606, filed 4/12/2001, of record).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 12/28/2006 and for reasons outlined below.

Applicants submit that the cited passages of Tennekoon et al do not disclose or suggest the claimed methods. The Examiner argues that a cell that can differentiate into oligodendrocytes and neurons is inherently a multipotent neuronal stem cell. However Tennekoon states at column 1, line 66 to column 2, line 2, that "[i]t is therefore an object of the present invention to provide a source for differentiated oligodendrocytes and neurons, respectively; that is independent of neural stem cell and conventional cell lines." Applicants submit that therefore Tennekoon's mesenchymal stromal cells are, not and do not include neural stem cells. Applicants submit that Tennekoon also states that neural stem cells have drawbacks and are difficult to obtain (see column 1, lines 56-63}. Applicants submit that Tennekoon teaches away from using neural stem cells. Applicants submit that Tennekoon does not disclose or suggest a method of producing oligodendrocytes from mammalian multipotent neural stem cells, comprising contacting the neural stem cells with at least one oligodendrocyte promoting factor under conditions that result in production of oligodendrocytes from the multipotent neural stem cells.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive.

The instant application discloses what Applicants intend as a neural stem cell in paragraph 0055:

A "multipotent neural stem cell", or "neural stem cell", is a stem cell in the neural cell lineage. A stem cell is a cell that is capable of reproducing itself. In other words, when a stem cell divides, at least some of the resulting daughter cells are also stem cells. Neural stem cells and their progeny are capable of differentiating into all the cell types in the neural cell lineage, including neurons, astrocytes and oligodendrocytes (astrocytes and oligodendrocytes are collectively called glial or glial cells). Therefore, the neural stem cells are multipotent neural stem cells. Multipotent neural stem cells are described, for example, in U.S. Pat. Nos. 5,750,376; 5,980,885 and 5,851,832 and 5,851,832.

Tennekoon does disclose difficulty in obtaining neural stem cells, disadvantages of their use and their goal of providing a source for differentiated oligodendrocytes in columns 1 and 2. Tennekoon use mesenchymal stromal cells and are able to differentiate them into oligodendrocytes. Since the instant disclosure discloses that "Neural stem cells and their progeny are capable of differentiating into all the cell types in the neural cell lineage, including neurons, astrocytes and oligodendrocytes" and the mesenchymal stromal cells do differentiate into oligodendrocytes, than the mesenchymal stromal cells are inherently neural stem cells in the neural cell lineage. If the mesenchymal stromal cells did not differentiate into oligodendrocytes or neurons they could not be identified as neural stem cells. A cell that is a parent of a differentiated neural cell (i.e. an oligodendrocyte) is inherently a neural stem cell even though it was isolated from bone marrow. Therefore the teaching of Tennekoon does disclose the

limitation of neural stem cell and it is not necessary to prove facts beyond those disclosed in Tennekoon in order to meet the claim limitations.

Election/Restrictions

It is noted that Applicants do not concede that the claims fail to comprise a special technical feature over U.S. Patent No. 6,673,606 (Tennekoon). However, since Tennekoon does anticipate the claimed methods as discussed above, the claims do not comprise a special technical feature over the prior art.

Applicant's arguments, see Remarks, filed 2/26/2007, with respect to claims 1-3 and 5-15 have been fully considered and are persuasive. The rejection of claims 1-3 and 5-15 under 35 U.S.C. 102(e) as being anticipated by Bjornson et al under has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tennekoon et al (of record) in view of Magil et al (U.S. Patent Application No. 20030171269, filed 10/23/2001).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 12/28/2006 and for reasons outlined below.

Applicants submit that claims 1 and 16 are not obvious based on Tennekoon in view of Magil at least because the cited portions of the references alone or in combination fail to recite each and every element of the creams. Applicants submit that Tennekoon mesenchymal stromal cells are not and do not include neural stem cells. Applicants submit that Tennekoon does not disclose or suggest the methods defined by claims 1 and 16. Applicants submit that Magil does not make up for the deficiencies of Tennekoon since Magil was only cited for describing EGF51N. Applicants submit that the cited portions of Tennekoon and Magil alone or in combination fail to disclose or suggest that EGF51N is a biological agent that can increase neural stem cell numbers. Applicants submit that the cited references also do not provide one of ordinary skill in the art with a reasonable expectation of success, Tennekoon states that neural stem cells have drawbacks and are difficult to obtain (see column 1, lines 56-63). Applicants submit that Tennekoon teaches away from using neural stem cells.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicant's arguments regarding Tennekoon have been discussed above. Briefly, since the instant disclosure discloses that "Neural stem cells and their progeny are capable of differentiating into all the cell types in the neural cell lineage, including neurons, astrocytes and oligodendrocytes" and the mesenchymal stromal cells do differentiate into oligodendrocytes, than the mesenchymal stromal cells are inherently neural stem cells in the neural cell lineage.

Although Applicants submit that the cited references also do not provide the skilled artisan with a reasonable expectation of success because Tennekoon states that neural stem cells have drawbacks and are difficult to obtain (see column 1, lines 56-63), Tennekoon does produce oligodendrocytes from the method taught using the stromal cells which constitutes success. Therefore, claims 1 and 16 are obvious based on Tennekoon in view of Magil.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571)272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
Examiner
5/14/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER